Autoimmune Myelofibrosis in Systemic Lupus Erythematosus Report of Two Cases and Review of the Literature

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Abstract Autoimmune myelofibrosis (AIMF) is a rare entity of steroid-responsive bone marrow fibrosis that accompanies a variety of autoimmune diseases, particularly systemic lupus erythematosus (SLE). Rarely it may occur in patients with autoimmune markers but no definable autoimmune disease (Primary-AIMF). We report the cases of two young women with SLE-associated AIMF (SLE-AIMF). The first patient was a young woman who had pancytopenia, massive splenomegaly and reticulin fibrosis in the marrow biopsy. The pancytopenia and splenomegaly resolved completely within weeks of treatment with corticosteroids. Repeat marrow biopsy showed marked regression of marrow fibrosis. The second patient was a young woman with fever, anasarca, bicytopenia and reticulin fibrosis in the marrow biopsy. Steroid therapy resulted in rapid clinical improvement and resolution of pancytopenia. A review of the literature revealed a total of 30 patients with SLE-AIMF reported to-date. Patients with SLE-AIMF are young women with SLE and blood cytopenia who are found to have increased bone marrow reticulin on marrow

biopsy. Steroid therapy results in rapid hematological recovery and regression of marrow fibrosis. Whether AIMF is one of several hematological complications of SLE, or represents a unique and distinct subset of patients with SLE is not clear. Prospective studies with longer follow-up are needed to better define the prevalence and clinical spectrum of SLE-AIMF.

Keywords Systemic lupus erythematosus · Myelofibrosis · Bone marrow · Autoimmunity

A variety of diseases both neoplastic and non-neoplastic, may cause bone marrow fibrosis by common and probably overlapping pathogenic mechanisms [1, 2]. Myeloproliferative neoplasms, certain lymphoproliferative disorders and epithelial malignancies with marrow involvement are widely recognized to cause marrow fibrosis. Less widely recognized is autoimmune myelofibrosis (AIMF) associated with systemic lupus erythematosus (SLE-AIMF) [3] and the recently described entity primary AIMF (Primary-AIMF) [4–8]. The clinical spectrum and the natural history of AIMF remain to be fully explored. We report the cases of two young women diagnosed with SLE-AIMF who had a rapid response to steroid therapy and review the literature.

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Case 1

A 22-year-old woman was admitted to the Hospital complaining of evening rise of temperature and shortness of breath of 3 months' duration, and hyperpigmentation of the nose. She denied alopecia, photosensitivity, Raynaud's phenomenon, oral ulceration, or arthralgia. She had been

amenorrheic for the past 3 months. She was diagnosed with hypothyroidism two years ago and was taking levothyroxine 100 µg daily.

Her examination revealed hyperpigmentation of the tip of the nose and *alae nasi*. Bilateral posterior cervical lymphadenopathy was present with the largest node measuring 1.5 cm. The spleen was palpable 11 cm below the left costal margin and 17 cm below the xiphoid. A pericardial rub was audible.

Her Hb was 5.9 g/dL, leukocytes $2.5 \times 10^9/L$, platelets $180 \times 10^9/L$ and reticulocytes 0.8 %. Blood smear examination showed normal red cell morphology and absence of leukoerythroblastosis. Urinalysis showed normal findings. Serum creatinine, total bilirubin, lactate dehydrogenase and TSH were within normal limits. The serum total protein was 9.6 g/dL and globulin 7.0 g/dL. Protein electrophoresis showed polyclonal hyperglobulinemia. Screen for antinuclear antibodies was positive. Anti-ds-DNA, anti-Sm, anti-RNP and anti-SSB antibodies were strongly positive. The direct antiglobulin test (DAT) was positive. The results of ELISA for HIV antibodies and a Montoux tuberculin skin test were negative. Computed tomographic scan of abdomen showed marked splenomegaly measuring 22 cm and pericardial effusion (Fig. 1). An excisional biopsy of cervical lymph node showed non-specific changes. Both pleural and ascitic fluid were transudates.

Bone marrow aspiration yielded extremely scanty material that showed areas of small lymphocyte infiltration (Fig. 2a); marrow trephine biopsy showed hypercellular

marrow, non-clustered megakaryocytes, normoblastic erythroid hyperplasia, normal myelopoiesis and grade-3 (modified Bauermeister scale) reticulin fibrosis (Fig. 2b). A test for JAK2 V617F mutation gave a negative result.

She was started on 1.5 mg/kg/d of prednisone. After 5 weeks of steroid therapy she was asymptomatic; the lymph nodes and spleen were not palpable. Her Hb increased to 12.4 g/dL and leukocytes increased to $13 \times 10^9/L$. A bone marrow biopsy done after 7 weeks of steroid therapy showed normal marrow morphology and grade-1 reticulin fibrosis (Fig. 2c); a repeat DAT result was negative. The total serum protein was 7.1 g/dL and serum globulin 3.1 g/dL. One year following her initial diagnosis with SLE-AIMF she developed proteinuria (4 g/24 h) and was diagnosed with membranoproliferative glomerulonephritis. Her spleen remains non-palpable.

Case 2

A 23-year-old woman was admitted to the Hospital with a dry cough and fever of 2 weeks' duration. One week before admission she developed puffiness of face, pedal edema and abdominal distention. Her past history was of hypothyroidism diagnosed 2 years previously. Her menstrual history was normal.

She was acutely ill, pale and febrile. She had a puffy face, pedal edema and ascites. There was no lymphadenopathy or splenomegaly.

Her Hb was 6.5 g/dL, leukocytes $6.0 \times 10^9/L$ with normal differential count, platelets $22 \times 10^9/L$ and reticulocytes 0.8 %. Blood smear examination showed normal red cell morphology and no nucleated red cells or immature myeloid cells. Results of urinalysis and liver function tests were normal. The serum creatinine was 1.0 mg/dL, lactate dehydrogenase 597 U/L, serum ferritin 1309 ng/mL and TSH 43 µIU/L. An ELISA for anti-nuclear antibodies was strongly positive; test for anti-ds-DNA antibodies and DAT were negative. The C3 complement level was normal. The results of ELISA for HIV antibodies were negative. Blood and urine cultures remained sterile.

Multiple attempts at bone marrow aspiration resulted in a dry-tap. Examination of marrow trephine biopsy showed normocellular marrow, increased non-clustered megakaryocytes, normal erythro-myelopoiesis, areas of stromal edema with dilated sinusoids and serous degeneration. Reticulin stain showed grade-3 (modified Bauermeister scale) reticulin fibrosis (Fig. 2d).

She was treated with packed red cell transfusion, amoxicillin-clavulanate and 2 mg/kg/d prednisone. There was prompt resolution of ascites, pleural effusion and pedal edema suggestive of capillary leak syndrome. She was discharged on the sixth hospital day. Following 3 weeks of

Fig. 1 Computed tomographic scan (coronal reconstruction) showing hepatosplenomegaly and pericardial effusion

Fig. 2 **a** Marrow smear showing small lymphocyte infiltrate. **b** Case 1. Section of bone marrow trephine at diagnosis showing MF-2 reticulin fibrosis (Gomori silver stain, $\times 400$). **c** Case 1. Section of bone marrow trephine showing marked regression of reticulin fibrosis

following steroid therapy (Gomori silver stain, $\times 400$). **d** Case 2. Section of bone marrow trephine showing MF-2 reticulin fibrosis (Gomori silver stain, $\times 400$)

steroid therapy she was asymptomatic. Her Hb was 10.5 g/dL, leukocytes $11.2 \times 10^9/L$, and platelets $120 \times 10^9/L$. At her 6-month follow-up she complained of malar rash and photosensitivity. Results of her complete blood count were normal. She was started on hydroxychloroquine 200 mg daily and continues to do well on prednisone 5 mg daily.

Discussion

The clinical and laboratory findings in our patients fulfill the 1997 update of the ARA criteria and the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria for the diagnosis of SLE [9]; the presence of bone marrow reticulin fibrosis and absence of other causes of bone marrow fibrosis established the diagnosis of SLE-AIMF in our patients.

The two patients reported here bring the number of patients with SLE-AIMF reported in the literature to 32 (Table 1). The mean age of the patients with SLE-AIMF

was 34 years (range 12–70 years) and 28 were female as expected in SLE. Patients with primary-AIMF are older with a mean age of 52 years [4–8].

Seventeen of 32 patients had pancytopenia and 13 patients had bicytopenia (40 %). Thrombocytopenia was present in all but two patients (patients 9 and 31, Table 1); splenomegaly was present in 14 of 29 patients (48 %). The prevalence of splenomegaly and thrombocytopenia is much lower (15 %) in unselected patients with SLE [10]. The DAT was positive in 10 out of 20 patients, three of whom had overt hemolytic anemia (patients 14, 19 and 27).

Hematological response to steroid therapy was observed in all but three patients (patients 13, 15 and 16, Table 1) and occurred within 2 weeks of starting treatment in a third of the patients. Six patients required IVIG, cyclophosphamide or azathioprine in addition to corticosteroids for response.

Although marked splenomegaly has been considered as an exclusion criterion for the diagnosis of AIMF [4, 5] our patient (case 1) had massive splenomegaly that regressed rapidly with steroid therapy; experience with two other

Table 1 Clinicopathological features, and regression of bone marrow fibrosis following treatment, in systemic lupus erythematosus patients with autoimmune myelofibrosis (1969–2014)

First author, year	Patient no.	Age, sex	Duration of SLE	Splenomegaly	Cytopenia	DAT	Dry Tap	Marrow fibrosis	Marrow fibrosis following therapy	Duration Of F/U
Lau, 1969	1	25, F	1 year	+	Pancytopenia	Neg	+	Col	No regression	3 months
Daly, 1983	2	16, F	C	+	Pancytopenia	Neg	+	Col	Marked regression	2 months
Nanji, 1984	3	28, M	4 years	+	Bicytopenia	Neg	No	Col	Died soon after admission	–
Kaelin, 1986	4	27, F	9 years	No	Thrombocytopenia	+	+	Ret	No regression	5 months
El Mouzan, 1988	5	13, F	C	+	Pancytopenia	+	+	Ret	No regression	16 months
Inoue, 1992	6	24, F	C	No	Bicytopenia	Neg	+	Ret	Complete regression	18 months
Foley-Nolan, 1992	7	20, F	C	No	Bicytopenia	+	+	Ret	Complete regression	1 year
Hirose, 1993	8	54, F	C	NR	Pancytopenia	NR	+	Ret	Marked regression	4 months
Borba, 1993	9	39, F	3 years	No	Bicytopenia	+	+	Ret	No regression	7 months
Paquette, 1994	10	68, M	C	No	Pancytopenia	NR	+	Ret	Regression	12 months
	11	27, F	C	+	Bicytopenia	+	+	“Fibrosis”	Regression	3 months
	12	23, F	9 years	+	Bicytopenia	NR	+	“Fibrosis”	Not investigated	NR
	13	56, F	9 months	No	Bicytopenia	Neg	NR	Ret	Not investigated	NR
	14	18, F	C	+	Bicytopenia	+	+	Ret	Not investigated	NR
	15	70, F	2 years	No	Pancytopenia	+	+	Col	Not investigated	6 months
	16	58, F	C	+	Pancytopenia	NR	+	Col	Not investigated	3 years
	17	69, F	3 years	No [†]	Bicytopenia	NR	+	Ret	Not investigated	NR
Agarwal, 1995	18	12, F	3 years	No	Thrombocytopenia	Neg	No	Ret	Complete regression	1 month
Ramakrishna, 1995	19	18, F	C	No	Bicytopenia	+	+	Ret	Regression	2 years
Aharon, 1997	20	54, F	C	+	Pancytopenia	NR	No	Col	Complete regression	3 months
Konstantopoulos, 1998	21	26, F	C	No	Pancytopenia	Neg	+	Ret	Marked regression	5 months
Vora, 1998	22	22, F	2 years	+	Pancytopenia	NR	+	Col	Marked regression	1 year
Durupt, 2000	23	29, F	3 years	NR	Pancytopenia	NR	+	Ret	Not investigated	9 months
Kiss, 2000	24	18, F	C	No	Pancytopenia	NR	+	Ret	Complete regression	22 months
Amital, 2003	25	54, F	C	+	Pancytopenia	NR	NR	Col	Marked regression	5 years
Azia, 2004	26	22, M	C	+	Pancytopenia	NR	+	Ret	Complete regression	3 months
Sarkar, 2009	27	45, M	C	No	Pancytopenia	+	No	Ret	Not investigated	1 month
Sacre, 2010	28	44, F	11 years	No	Bicytopenia	Neg	NR	Ret	Not investigated	3 years
Chalayer, 2014	29	22, F	9 years	+	Pancytopenia	Neg	+	“Fibrosis”	Not investigated	17 months
Fechner, 2014	30	49, F	15 years	NR	Pancytopenia	NR	NR	Ret	Not investigated	NR
Present report, 2014	31	22, F	C	+	Bicytopenia	+	+	Ret	Marked regression	12 months
	32	23, F	C	No	Bicytopenia	Neg	+	Ret	Not investigated	17 months

[†] Patient had previous splenectomy for immune thrombocytopenia

SLE systemic lupus erythematosus, DAT direct antiglobulin test, F/U follow-up, Col collagen fibrosis, C diagnosis of SLE and myelofibrosis made concomitantly, Ret reticulin fibrosis, NR not reported, Neg negative

similar cases [7, 11] suggests that marked splenomegaly that regresses rapidly following steroid therapy may be a rare manifestation of AIMF.

Small hypolobated bone marrow megakaryocytes described by Bass et al. [4] in patients with primary-AIMF are not a feature of SLE-AIMF. Paquette et al. [3] described clustered megakaryocytes in bone marrow biopsies as an “invariable” feature in SLE-AIMF. Subsequent reports make no mention of megakaryocyte clustering in bone marrow biopsies in SLE-AIMF. Some of these inconsistencies may be related to the small number of patients studied.

Reactive lymphoid infiltration of the marrow is considered by some investigators to be one of the required criteria for the diagnosis of primary-AIMF [4, 5]. This finding was present in only four of the 32 patients with SLE-AIMF (patients 1, 24, 27 and 31).

Bone marrow fibrosis was qualified as collagen fibrosis in eight patients, as reticulin fibrosis in 21 patients and not further specified in three. Regression of collagen fibrosis occurred following steroid therapy (with IVIG added in two cases) in four of the nine patients (Table 1). Regression of reticulin fibrosis with steroid therapy occurred in 10 of the 13 patients in whom bone marrow biopsy was repeated. The development of bone marrow fibrosis may not be related to the duration of prior SLE. The diagnosis of SLE was made concomitantly with the diagnosis of bone marrow fibrosis in 18 of 32 patients. The duration of SLE prior to the diagnosis of AIMF in the others ranged from 9 months to 15 years.

The reported prevalence of increased marrow reticulin in SLE patients with blood cytopenia ranged from 12 % [12] to more than 67 % [13, 14]. Feng et al. [15] reported bone marrow abnormalities in 23 patients with SLE and pancytopenia; no mention is made of bone marrow fibrosis in the patients studied. The reason for the wide variation in the reported prevalence of bone marrow fibrosis in these reports is not clear.

The relative contributions of fibrosis per se and the underlying disease (SLE) to the bone marrow dysfunction remain unclear [1]. The impact of AIMF on the course of the disease (SLE) if any is not clear due to limited clinical information and short follow-up in many patients.

Clinical and experimental data suggest common and overlapping pathogenic mechanisms of fibrogenesis in various organs including the bone marrow [16, 17]. The activation of fibroblasts to myofibroblasts is mediated by cytokines and chemokines. Principal among these are transforming growth factor beta (TGF- β) and platelet derived growth factor (PDGF). Immune complexes, uncharacterized autoantibodies, or inflammatory cytokines might interact with megakaryocytes and result in secretion of profibrotic substances, principally TGF- β that

activate resident fibroblasts to secrete reticulin and collagen.

Circulating immune complexes have been implicated in the fibrogenic response in chronic idiopathic myelofibrosis as far back as 1981 [18]. Barcellini et al. [19] recently reported increased incidence of autoimmune markers and elevated levels of TGF- β in chronic idiopathic myelofibrosis. Elevated serum levels of TGF- β and a marked increase in TGF- β production by blood monocytes have been described recently in a patient with primary-AIMF [20].

The rarity of reports of AIMF in SLE lacks a clear explanation. Under-diagnosis may be a part explanation because it has not been systematically investigated [2]. Genetic and epigenetic factors have been invoked to explain individual susceptibility to fibrosis. Results of studies exploring the link between TGF- β polymorphisms and fibrosis susceptibility have been conflicting [21].

Conflict of interest The authors declare that they have no conflict of interest to declare.

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